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(54) Title: POLYPROLYL INHIBITORS OF CYCLOPHILIN

(57) Abstract

This invention relates to neurotrophic low molecular weight, small molecule peptidic cyclophilin inhibitor compounds having an affinity for cyclophilin-type immunophilins, and their use as inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity.

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POLYPROLYL INHIBITORS OF CYCLOPHILIN

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to neurotrophic low molecular weight, small molecule peptidic cyclophilin inhibitor compounds having an affinity for cyclophilin-type immunophilins, and their use as inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity.

2. Description of Related Art

The term immunophilin refers to a number of proteins that serve as receptors for the principal immunosuppressant drugs, cyclosporin A (CsA), FK506 and rapamycin. Known classes of immunophilins are cyclophilins and FK506 binding proteins, or FKBPs. Cyclosporin A binds to cyclophilin A while FK506 and rapamycin bind to FKBP12. These immunophilin-drug complexes interface with various intracellular signal transduction systems, especially the immune and nervous systems.

Immunophilins are known to have peptidyl-prolyl isomerase (PPIase), or rotamase, enzyme activity. It has been determined that rotamase enzyme activity plays a role in the catalyzation of the interconversion of the *cis* and *trans* isomers of peptide and protein substrates for the immunophilin

proteins.

Immunophilins were originally discovered and studied in the immune tissue. It was initially postulated by those skilled in the art that inhibition of the immunophilins' rotamase activity leads to inhibition of T-cell proliferation, thereby causing the immunosuppressive activity exhibited by immunosuppressant drugs, such as cyclosporin A, FK506 and rapamycin. Further study has shown that the inhibition of rotamase activity, in and of itself, does not result in immunosuppressive activity. Schreiber et al., *Science*, 1990, vol. 250, pp. 556-559. Instead, immunosuppression appears to stem from the formulation of a complex of immunosuppressant drug and immunophilin. It has been shown that immunophilin-drug complexes interact with ternary protein targets as their mode of action. Schreiber et al., *Cell*, 1991, vol. 66, pp. 807-815. In the case of FKBP-FK506 and cyclophilin-CsA, the immunophilin-drug complexes bind to the enzyme calcineurin and inhibit the T-cell receptor signalling which leads to T-cell proliferation. Similarly, the immunophilin-drug complex of FKBP-rapamycin interacts with the RAFT1/FRAP protein and inhibits the IL-2 receptor signalling.

Immunophilins have been found to be present at high concentrations in the central nervous system.

Immunophilins are enriched 10-50 times more in the central nervous system than in the immune system. Within neural tissues, immunophilins appear to influence nitric oxide synthesis, neurotransmitter release and neuronal process extension.

Surprisingly, it has been found that certain low molecular weight, small peptidic sequences with a high affinity for cyclophilin A are potent rotamase inhibitors and exhibit excellent neurotrophic effects. These findings suggest the use of cyclophilin rotamase inhibitors in treating various peripheral neuropathies and enhancing neuronal regrowth in the central nervous system (CNS). Studies have demonstrated that neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may occur due to the loss, or decreased availability, of a neurotrophic substance specific for a particular population of neurons affected in the disorder.

Several neurotrophic factors affecting specific neuronal populations in the central nervous system have been identified. For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of nerve growth factor (NGF). It has thus been proposed to treat SDAT patients with exogenous nerve growth factor or other neurotrophic proteins, such as brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor and

neurotropin-3, to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressant drugs exhibit a number of potentially serious side effects including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., *J. Am. Soc. Nephrol.*, 1991, 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina, such as non-localized headaches (De Groen et al., *N. Engl. J. Med.*, 1987, 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., *N. Engl. J. Med.*, 1989, 321:1725).

In order to prevent the side effects associated with the use of the immunosuppressant compounds, the present invention provides non-immunosuppressive compounds containing low molecular weight, small molecule peptidic sequences for enhancing neurite outgrowth, and promoting neuronal growth and regeneration in various neuropathological situations where neuronal repair can be facilitated, including:

peripheral nerve damage caused by physical injury or disease state such as diabetes; physical damage to the central nervous system (spinal cord and brain); brain damage associated with stroke; and neurological disorders relating to neurodegeneration, such as Parkinson's disease, SDAT (Alzheimer's disease), and amyotrophic lateral sclerosis.

SUMMARY OF THE INVENTION

The present invention relates to neurotrophic low molecular weight, small molecule peptidic cyclophilin inhibitor compounds having an affinity for cyclophilin-type immunophilins. Once bound to these proteins, the neurotrophic compounds are potent inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl isomerase, or rotamase, enzyme activity. A key feature of the compounds of the present invention is that they do not exert any significant immunosuppressive activity in addition to their neurotrophic activity.

Specifically, the invention relates to a compound of formula I (SEQ ID NOS. 1-2):

X-Pro-A3-A1-Pro-A2-Z I

wherein:

A3 is either a direct bond or a naturally

occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

A1 and A2 are naturally occurring amino acids independently selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

X is a pharmaceutically acceptable N-terminal; and

Z is a pharmaceutically acceptable C-terminal.

In a preferred embodiment, the N-terminal is acetyl and the C-terminal is amino.

In another preferred embodiment, A3 is proline (Pro) (SEQ ID NO. 3).

In a most preferred embodiment, A3 is proline (Pro); A1 is selected from the group consisting of tyrosine (Tyr) and phenylalanine (Phe); and A2 is

selected from the group consisting of alanine (Ala), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), isoleucine (Ile), lysine (Lys), leucine (Leu), proline (Pro), valine (Val) and tyrosine (Tyr) (SEQ ID NOS. 4-23).

The present invention also relates to a method of effecting a neuronal activity in an animal, comprising:

administering to the animal an effective amount of a neurotrophic compound having an affinity for a cyclophilin-type immunophilin, wherein the immunophilin exhibits rotamase activity and the neurotrophic compound inhibits the rotamase activity of the immunophilin.

In a preferred embodiment, the neuronal activity is treatment of a neurological disorder selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

In a most preferred embodiment, the neuronal activity is treatment of a neurological disorder relating to neurodegeneration, said disorder selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

The present invention further relates to a

pharmaceutical composition comprising:

(i) a therapeutically effective amount of a neurotrophic compound of formula I (SEQ ID NOS. 1-2):

X-Pro-A3-A1-Pro-A2-Z I

and

(ii) a pharmaceutically acceptable carrier,

wherein:

A3 is either a direct bond or a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

A1 and A2 are naturally occurring amino acids independently selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

X is a pharmaceutically acceptable N-terminal; and

Z is a pharmaceutically acceptable C-terminal.

In a preferred embodiment, the N-terminal is acetyl and the C-terminal is amino.

In another preferred embodiment, A3 is proline (Pro) (SEQ ID NO. 3).

In a most preferred embodiment, A3 is proline (Pro); A1 is selected from the group consisting of tyrosine (Tyr) and phenylalanine (Phe); and A2 is selected from the group consisting of alanine (Ala), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), isoleucine (Ile), lysine (Lys), leucine (Leu), proline (Pro), valine (Val) and tyrosine (Tyr) (SEQ ID NOS. 4-23).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the extent of inhibition of cyclophilin A by the tetrapeptides of Table I.

FIG. 2 shows the extent of inhibition of cyclophilin A by the pentapeptides of Table II.

FIG. 3 shows the extent inhibition of cyclophilin A by the pentapeptides of Table III.

FIG. 4 shows the promotion of neurite outgrowth in chick sensory neurons by Ac-Pro-Gly-Pro-Phe-NH_2 at 1 mM.

FIG. 5 shows the promotion of neurite outgrowth

in chick sensory neurons by Ac-Pro-Ala-Pro-Ala-NH_2 at 1 mM.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Alkyl" means a branched or unbranched saturated hydrocarbon chain containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like, unless otherwise indicated.

"Alkoxy" means the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to 3 carbon atoms.

"Halo" means fluoro, chloro, bromo, or iodo, unless otherwise indicated.

"Phenyl" includes all possible isomeric phenyl radicals, optionally monosubstituted or multi-substituted with substituents selected from the group consisting of alkyl, alkoxy, hydroxy, halo, and haloalkyl.

"Treatment" covers any treatment of a disease and/or condition in an animal, particularly a human, and includes:

(i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diag-

nosed as having it;

(ii) inhibiting the disease and/or condition, i.e., arresting its development; and

(iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

Compound of the Invention

The neurotrophic low molecular weight, small molecule peptidic cyclophilin inhibitor compounds of the present invention have an affinity for cyclosporin A binding proteins such as cyclophilin A. When the neurotrophic compounds are bound to cyclophilin, they have been found to inhibit the prolyl-peptidyl *cis-trans* isomerase activity, or rotamase, activity of the binding protein and unexpectedly stimulate neurite growth.

In particular, the present invention relates to a compound of formula I (SEQ ID NOS. 1-2):

X-Pro-A3-A1-Pro-A2-Z I

wherein:

A3 is either a direct bond or a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine

(Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

A1 and A2 are naturally occurring amino acids independently selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

X is a pharmaceutically acceptable N-terminal; and

Z is a pharmaceutically acceptable C-terminal.

In a preferred embodiment, A3 is proline (Pro) (SEQ ID NO. 3).

In a most preferred embodiment, A3 is proline (Pro); A1 is selected from the group consisting of tyrosine (Tyr) and phenylalanine (Phe); and A2 is selected from the group consisting of alanine (Ala), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), isoleucine (Ile), lysine (Lys), leucine (Leu), proline (Pro), valine (Val) and tyrosine (Tyr) (SEQ ID NOS. 4-23).

The N-terminal (amino terminal) may be any protecting group for amino. Examples of an N-terminal

include without limitation: carbamates such as methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, and 4-methoxyphenacyl carbamate; substituted ethyl carbamates such as 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2,-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'-and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*- chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, and diphenylmethyl carbamate; assisted cleavage carbamates such as 2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxylboryl)benzyl, 5-benzisoxazolylmethyl, and 2-(trifluoromethyl)-6-chromonylmethyl carbamate; photolytic cleavage carbamates such as *m*-nitrophenyl, 3,5-dimethoxybenzyl, o-nitrobenzyl, 3,4-dimethoxy-6-

nitrobenzyl, and phenyl(o-nitrophenyl)methyl) carbamate; urea-type carbamate derivatives such as phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, and *N'*-phenylaminothiocarbonyl derivative; miscellaneous carbamates such as *t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, o-(*N,N*-dimethylcarboxamido)benzyl, *N*-o-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one carbamate; cyclic imide carbamate derivatives such as *N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl carbamate; *N*-alkyl and *N*-aryl amines such as *N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, and *N*-2-picolylamine *N'*-oxide amine; imine derivatives such as *N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-

methoxybenzylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*-(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, and *N*-cyclohexylidene; enamine derivatives such as *N*-(5,5-dimethyl)-3-oxo-1-cyclohexenyl) enamine; *N*-hetero atom derivatives such as *N*-metal (for example, *N*-borane, *N*-diphenylborinic acid, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate), N-N (for example, *N*-nitro, *N*-nitroso, and *N*-oxide), N-P (for example, *N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, and *N*-diphenyl phosphoryl), N-Si, and N-S (for example, N-sulfenyl such as *N*-benzenesulfenyl, *N*-o-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl) derivatives; and *N*-sulfonyl such as *N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-

methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-ß-trimethylsilylethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-trifluoromethylsulfonyl, and *N*-phenacylsulfonyl).

The C-terminal (carboxyl terminal) may be any protecting group for carboxyl. Examples of a C-terminal include without limitation: substituted methyl esters such as 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, phenacyl (for example, *p*-bromophenacyl, α-methylphenacyl, and *p*-methoxyphenacyl), carboxamidomethyl, and *N*-phthalimidomethyl ester; 2-substituted ethyl esters such as 2,2,2-trichloroethyl, 2-haloethyl, ω-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, t-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, α-methylcinnamyl, phenyl, *p*-(methylmercapto)phenyl, and benzyl ester; substituted benzyl esters such as triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 5-dibenzosuberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl,

p-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, 4-picolyl, and *p*-[illegible]-benzyl ester; silyl esters such as trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, and di-*t*-butylmethylsilyl ester; activated esters such as thiols; ester derivatives such as oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl esters, and pentaaminocobalt(III) complex; stannyl esters such as tri-ethylstannyl and tri-*n*-butylstannyl ester; amides such as *N,N*-dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, *N*-7-nitroindolyl, *N*-8-nitro-1,2,3,4-tetrahydroquinolyl, and *p*-[illegible]-benzenesulfonamide; and hydrazides such as *N*-phenyl and *N,N'*-diisopropyl hydrazide.

In a preferred embodiment, the N-terminal is acetyl and the C-terminal is amino.

The compounds of the present invention may be synthesized according to any procedure known in the art. For illustration, Example I, below, sets forth a representative procedure for synthesizing some of the inventive compounds.

Method of Use

The compounds of the present invention have an affinity for cyclosporin-type binding proteins,

particularly cyclophilin A, which is present in the brain. When the compounds bind to cyclophilin A in the brain, they exhibit excellent neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the prevention of neurodegeneration, and the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral neuropathies. For the foregoing reasons, the present invention further relates to a method of effecting a neuronal activity in an animal, comprising:

administering to the animal an effective amount of a neurotrophic compound having an affinity for a cyclophilin-type immunophilin, wherein the immunophilin exhibits rotamase activity and the neurotrophic compound inhibits the rotamase activity of the immunophilin.

In a preferred embodiment, the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia; glossopharyngeal neuralgia; Bell's Palsy; myasthenia gravis; muscular dystrophy; amyotrophic lateral sclerosis; progressive muscular atrophy; progressive

bulbar inherited muscular atrophy; herniated, ruptured or prolapsed invertebrate disk syndromes; cervical spondylosis; plexus disorders; thoracic outlet destruction syndromes; peripheral neuropathies such as those caused by lead, dapsone, ticks, porphyria, or Guillain-Barré syndrome; Alzheimer's disease; and Parkinson's disease.

The compounds of the present invention are particularly useful for treating a neurological disorder selected from the group consisting of: peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration. Examples of neurological disorders relating to neurodegeneration are Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

For these purposes, the compounds may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal and intracranial injection or infusion

techniques.

To be effective therapeutically as central nervous system targets, the compounds should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular route.

The compounds may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any bland fixed oil such as a synthetic mono- or di-glyceride may be employed. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain

alcohol diluents or dispersants.

Additionally, the compounds may be administered orally in the form of capsules, tablets, aqueous suspensions or solutions. Tablets may contain carriers such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient. The oral dosage forms may further contain sweetening and/or flavoring and/or coloring agents.

The compounds may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

Furthermore, the compounds may be administered topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations can be readily prepared for each of these areas.

For topical application to the eye, or ophthalmic

use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as a solution in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, the compounds may be formulated into ointments, such as petrolatum, for ophthalmic use.

For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Topical application to the lower intestinal tract can be effected in a rectal suppository formulations (see above) or in suitable enema formulations.

Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex, and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration.

The compounds can be administered with other neurotrophic agents such as neurotrophic growth factor (NGF), glial derived growth factor, brain derived growth factor, ciliary neurotrophic factor, and neurotropin-3. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

Pharmaceutical Composition

The compounds of present invention can be formulated into pharmaceutical compositions for the various uses described above. Accordingly, the present invention also relates to a pharmaceutical composition comprising:

(i) a therapeutically effective amount of a

neurotrophic compound of formula I (SEQ ID NOS. 1-2):

X-Pro-A3-A1-Pro-A2-Z I

and

(ii) a pharmaceutically acceptable carrier, wherein:

A3 is either a direct bond or a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

A1 and A2 are naturally occurring amino acids independently selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

X is a pharmaceutically acceptable N-terminal; and

Z is a pharmaceutically acceptable C-terminal.

In a preferred embodiment, the N-terminal is acetyl and the C-terminal is amino.

In another preferred embodiment, A3 is proline (Pro) (SEQ ID NO. 3).

In a most preferred embodiment, A3 is proline (Pro); A1 is selected from the group consisting of tyrosine (Tyr) and phenylalanine (Phe); and A2 is selected from the group consisting of alanine (Ala), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), isoleucine (Ile), lysine (Lys), leucine (Leu), proline (Pro), valine (Val) and tyrosine (Tyr) (SEQ ID NOS. 4-23).

The above discussion relating to the administration of the compound also applies to the pharmaceutical composition.

EXAMPLES

The following examples are illustrative of the present invention and are not intended to be limitations thereon. All polymer molecular weights are mean average molecular weights. Unless otherwise specified, all percentages are based on 100% percent by weight of the final compound or pharmaceutical composition.

EXAMPLE I

Synthesis of Peptides

Rink resin 0.25 g (0.44 meq/g) was transferred to

a reactor column and washed with dimethyl formamide (DMF) (3x5 min) followed by 50% piperidine in DMF (2x10 min) to remove protecting group 9-fluorenylmethoxycarbonyl (Fmoc). The resin was washed with DMF (5x5 min) and a first amino acid was added. For Ac-Pro-Gly-Pro-Phe-NH_2 (SEQ ID NO. 1), the first protected amino acid Fmoc-Phe (0.25 mmol) was dissolved together with 1-hydroxybenzo-triazole (HOBt; 0.25 mmol) in 2.5 ml DMF for pre-activation (3 min) followed by benzotriazolyloxy-(tris)dimethylamino-phosphonium hexafluorophosphate (BOP; 0.25 mmole) and 4-methylmorpholine (NMM; 0.375 mmole). The mixture was immediately poured into the reactor column and shaken for 2 hours. After 3x5 min DMF washing, negative color test for residual amine was obtained. The DMF wash was repeated and the subsequent residues (Fmoc-Pro, Fmoc-Gly, Fmoc-Pro) were added using the same deprotection, washing, coupling, washing cycle until all designed amino acids for the sequence had been connected. After the last amino acid was coupled, the Fmoc was removed by 50% piperidine in DMF (2x10 min) as before followed by DMF washing (5x5 min). The resin was acetylated of terminal amino group with 2 ml mixture of DMF: acetic anhydride: N-ethyldiisopropylamine = 193:6:1 (v/v/v) for 90 minutes at room temperature. The final peptide resin was washed with DMF (3x5 min), t-amyl alcohol (2x3 min), acetic acid (2x3 min), t-amyl alcohol (2x3 min), ether

(3x3 min), and dried in high vacuum overnight. The dried peptide resin was treated with 2 ml TFA:Phenol:H_2O = 90:5:5 for 2 hours at room temperature. The resin was filtered, washed thoroughly with TFA and the total filtrate evaporated under N_2. Methyl t-butyl ether (50 mL) was added to the residue and the resultant white precipitate was collected after centrifugation. The NMR spectrum was consistent with the expected structure.

EXAMPLE II

Tetrapeptide and Pentapeptide Combinatorial Libraries

The unexpected preference of poly-proline substrates for cyclophilin and the potent neurotrophic activity of the substrates were discovered using combinatorial peptide libraries to map the substrate specificity of the enzyme cyclophilin. Pools of tetrapeptide and pentapeptide substrates were generated as described in the literature (Houghten et al., *Nature*, 1991, vol. 354, pp. 84-86) and their potencies in binding to cyclophilin A were evaluated by examining the inhibition of peptidyl prolyl-isomerase activity. Positional scanning technique was used to determine the optimal amino acid(s) for each position of the tetra- or pentapeptide.

The following Tables I-III list the tetrapeptide and pentapeptide substrates that were tested. A1',

A2' and A3' in Tables I-III denote equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine).

TABLE I

TETRAPEPTIDE COMBINATORIAL LIBRARY # 1

Seq. Id. No.	Peptide Sequence	Number of Components	Av. Mol. Wt.
24	Ac-Ala-A1'-Pro-A2'-NH_2	324	407
25	Ac-Asp-A1'-Pro-A2'-NH_2	"	"
26	Ac-Glu-A1'-Pro-A2'-NH_2	"	"
27	Ac-Phe-A1'-Pro-A2'-NH_2	"	"
28	Ac-Gly-A1'-Pro-A2'-NH_2	"	"
29	Ac-His-A1'-Pro-A2'-NH_2	"	"
30	Ac-Ile-A1'-Pro-A2'-NH_2	"	"
31	Ac-Lys-A1'-Pro-A2'-NH_2	"	"
32	Ac-Leu-A1'-Pro-A2'-NH_2	"	"
33	Ac-Met-A1'-Pro-A2'-NH_2	"	"
34	Ac-Asn-A1'-Pro-A2'-NH_2	"	"
35	Ac-Pro-A1'-Pro-A2'-NH_2	"	"
36	Ac-Gln-A1'-Pro-A2'-NH_2	"	"
37	Ac-Arg-A1'-Pro-A2'-NH_2	"	"
38	Ac-Ser-A1'-Pro-A2'-NH_2	"	"
39	Ac-Thr-A1'-Pro-A2'-NH_2	"	"
40	Ac-Val-A1'-Pro-A2'-NH_2	"	"
41	Ac-Tyr-A1'-Pro-A2'-NH_2	"	"

TABLE II

PENTAPEPTIDE COMBINATORIAL LIBRARY # 1

Seq. Id. No.	Peptide Sequence	Mass (mg)
42	Ac-Ala-A3'-A1'-Pro-A2'-NH_2	26.5
43	Ac-Asp-A3'-A1'-Pro-A2'-NH_2	38.2
44	Ac-Glu-A3'-A1'-Pro-A2'-NH_2	47.1
45	Ac-Phe-A3'-A1'-Pro-A2'-NH_2	16.7
46	Ac-Gly-A3'-A1'-Pro-A2'-NH_2	34.3
47	Ac-His-A3'-A1'-Pro-A2'-NH_2	48.9
48	Ac-Ile-A3'-A1'-Pro-A2'-NH_2	35.0
49	Ac-Lys-A3'-A1'-Pro-A2'-NH_2	34.5
50	Ac-Leu-A3'-A1'-Pro-A2'-NH_2	6.8
51	Ac-Met-A3'-A1'-Pro-A2'-NH_2	22.4
52	Ac-Asn-A3'-A1'-Pro-A2'-NH_2	29.3
53	Ac-Pro-A3'-A1'-Pro-A2'-NH_2	9.5
54	Ac-Gln-A3'-A1'-Pro-A2'-NH_2	42.4
55	Ac-Arg-A3'-A1'-Pro-A2'-NH_2	43.3
56	Ac-Ser-A3'-A1'-Pro-A2'-NH_2	39.6
57	Ac-Thr-A3'-A1'-Pro-A2'-NH_2	30.2
58	Ac-Val-A3'-A1'-Pro-A2'-NH_2	22.5
59	Ac-Tyr-A3'-A1'-Pro-A2'-NH_2	41.0

TABLE III

PENTAPEPTIDE COMBINATORIAL LIBRARY # 3

Seq. Id. No.	Peptide Sequence	Avg. Mol. Wt.
60	Ac-Pro-Pro-Ala-Pro-A2'-NH_2	536.89
61	Ac-Pro-Pro-Glu-Pro-A2'-NH_2	594.89
62	Ac-Pro-Pro-Phe-Pro-A2'-NH_2	612.89
63	Ac-Pro-Pro-Gly-Pro-A2'-NH_2	522.89
64	Ac-Pro-Pro-Ile-Pro-A2'-NH_2	578.89
65	Ac-Pro-Pro-Lys-Pro-A2'-NH_2	593.89
66	Ac-Pro-Pro-Leu-Pro-A2'-NH_2	578.89
67	Ac-Pro-Pro-Pro-Pro-A2'-NH_2	562.89
68	Ac-Pro-Pro-Val-Pro-A2'-NH_2	564.89
69	Ac-Pro-Pro-Tyr-Pro-A2'-NH_2	628.89

EXAMPLE III

Ki Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the inventive compounds can be evaluated by known methods described in the literature (Harding, et al., *Nature*, 1989, 341:758-760; Holt et al. *J. Am. Chem. Soc.*, 115:9923-9938). These values are obtained as apparent Ki's and are presented for the compounds in Tables I-III. The *cis-trans* isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases *para*-nitroanilide from

the *trans* form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent Ki values. The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

Peptidic substrates were generated in pools as described above. Representative data for the evaluation of these combinatorial libraries is shown in FIGS. 1-3. FIG. 1 shows data from the tetrapeptide of the type Ac-X'-A1'-Pro-A2'-NH_2, where X' is a specifically defined amino acid and A1' and A2' are equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine). The inhibition curves demonstrate that proline and tyrosine, particularly proline, are preferred in the first position; that is, the preferred tetrapeptide inhibitors of cyclophilin A are of the form Ac-Pro-A1'-Pro-A2'-NH_2 or Ac-Tyr-A1'-Pro-A2'-NH_2. Table IV, below, gives IC_{50} values for the preferred mixtures.

TABLE IV

INHIBITION OF CYCLOPHILIN A

Seq. Id. No.	Peptide Sequence	Inhibition

		Curve (IC_{50})
35	Ac-Pro-A1'-Pro-A2'-NH_2	1 μM
41	Ac-Tyr-A1'-Pro-A2'-NH_2	12 μM

All other members of this library were much less active, indicating a high degree of specificity exhibited by cyclophilin, and that substrates containing more than one proline are preferred.

Similarly, FIG. 2 demonstrates that in the pentapeptide library, Ac-X'-A3'-A1'-Pro-A2'-NH_2, the preferred sequence motif is Ac-Pro-A3'-A1'-Pro-A2'-NH_2. These results demonstrate that cyclophilin A manifests a preference for polyprolyl substrates. This substrate specificity of cyclophilin A is completely unexpected. Data for a representative subsequent pentapeptide library is shown in FIG. 3.

EXAMPLE IV

Chick Dorsal Root Ganglion

Cultures and Neurite Outgrowth

The neurotrophic effects of the cyclophilin inhibitors were demonstrated by evaluating the ability of the compounds to promote neurite outgrowth in cultured chick sensory neurons from dorsal root ganglia. Dorsal root ganglia were dissected from chick embryos of ten day gestation. Whole ganglion explants were cultured on thin layer Matrigel-coated 12 well plates with Liebovitz L15 plus high glucose

media supplemented with 2 mM glutamine and 10% fetal calf serum, and also containing 10 μM cytosine ß-D arabinofuranoside (Ara C) at 37°C in an environment containing 5% CO_2. Twenty-four hours later, the DRGs were treated with various concentrations of nerve growth factor, immunophilin ligands or combinations of NFG plus drugs. Forty-eight hours after drug treatment, the ganglia were visualized under phase contrast or Hoffman Modulation contrast with a Zeiss Axiovert inverted microscope. Photomicrographs of the explants were made, and neurite outgrowth was quantitated. Neurites longer than the DRG diameter were counted as positive, with total number of neurites quantitated per each experimental condition. Three to four DRGs are cultured per well, and each treatment was performed in duplicate.

The maximal increase in the number of processes, their length and branching is quite similar at maximally effective contractions of the cyclophilin ligands and of NGF (100 ng/ml). With progressively increasing concentrations of the various drugs, one observes a larger number of processes, more extensive branching and a greater length of individual processes.

FIG. 4 shows the action of Ac-Pro-Gly-Pro-Phe-NH_2 on chick sensory neurons; at 1 mM concentration, the compounds exert powerful neurotrophic effects, as seen by the eliciting of long fibers from the cell body.

Similarly, FIG. 5 shows the potent neurotrophic effects of Ac-Pro-Ala-Pro-Ala-NH_2 on these neuronal cultures.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
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WEI, Ling
STEINER, Joseph P.
(ii) TITLE OF INVENTION: Polyprolyl Inhibitors of Cyclophilin
(iii) NUMBER OF SEQUENCES: 69
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(C) CITY: Washington, D.C.
(D) STATE:
(E) COUNTRY: U.S.A.
(F) ZIP: 20006-1203
(v) COMPUTER READABLE FORM
(A) MEDIUM TYPE: Diskette, 3.5 inch, 1.4 Mb storage
(B) COMPUTER: IBM PC/XT/AT compatible
(C) OPERATING SYSTEM: MS-DOS 6.0
(D) SOFTWARE: Word Perfect 5.1
(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: (not yet assigned)
(B) FILING DATE: December 4, 1997
(C) CLASSIFICATION: (not yet assigned)
(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: NATH, Gary M.
(B) REGISTRATION NUMBER: 26,965
(C) REFERENCE/DOCKET NUMBER: 23136
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(A) TELEPHONE: (202) 775-8383
(B) TELEFAX: (202) 775-8396

(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: independently selected from the group consisting of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Tyr, Cys and Trp
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Pro Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: independently selected from the group consisting of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Tyr, Cys and Trp
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Pro Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 3 and 5
(D) OTHER INFORMATION: independently selected from the group consisting of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Tyr, Cys and Trp
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Pro Pro Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Pro Pro Tyr Pro Ala
1 5

(2) INFORMATION FOR SEQ ID NO:5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Pro Pro Tyr Pro Glu
1 5

(2) INFORMATION FOR SEQ ID NO:6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Pro Pro Tyr Pro Phe
1 5

(2) INFORMATION FOR SEQ ID NO:7:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Pro Pro Tyr Pro Gly
1 5

(2) INFORMATION FOR SEQ ID NO:8:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Pro Pro Tyr Pro Ile
1 5

(2) INFORMATION FOR SEQ ID NO:9:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Pro Pro Tyr Pro Lys
1 5

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Pro Pro Tyr Pro Leu
1 5

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Pro Pro Tyr Pro Pro
1 5

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Pro Pro Tyr Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Pro Pro Tyr Pro Tyr
1 5

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Pro Pro Phe Pro Ala
1 5

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Pro Pro Phe Pro Glu
1 5

(2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Pro Pro Phe Pro Phe
1 5

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Pro Pro Phe Pro Gly
1 5

(2) INFORMATION FOR SEQ ID NO:18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Pro Pro Phe Pro Ile
1 5

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Pro Pro Phe Pro Lys
1 5

(2) INFORMATION FOR SEQ ID NO:20:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Pro Pro Phe Pro Leu
1 5

(2) INFORMATION FOR SEQ ID NO:21:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Pro Pro Phe Pro Pro
1 5

(2) INFORMATION FOR SEQ ID NO:22:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Pro Pro Phe Pro Val
1 5

(2) INFORMATION FOR SEQ ID NO:23:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Pro Pro Phe Pro Tyr
1 5

(2) INFORMATION FOR SEQ ID NO:24:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Ala Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:25:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Asp Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:26:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Glu Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:27:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Phe Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Gly Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

His Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:30:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4

(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ile Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Lys Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Leu Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Asn Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Pro Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:36:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Gln Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:37:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Arg Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:38:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Ser Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:39:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Thr Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Val Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:41:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2 and 4
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Tyr Xaa Pro Xaa

(2) INFORMATION FOR SEQ ID NO:42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ala Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa

(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Asp Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:44:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Glu Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:45:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Phe Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:46:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures

of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Gly Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:47:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

His Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:48:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Ile Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring

amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Lys Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:50:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Leu Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:51:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Met Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:52:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Asn Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:53:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Pro Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:54:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Gln Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:55:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Arg Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:56:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ser Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:57:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Thr Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:58:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Val Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:59:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: positions 2, 3 and 5
(D) OTHER INFORMATION: equimolar mixtures of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Tyr Xaa Xaa Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:60:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Pro Pro Ala Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:61:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Pro Pro Glu Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:62:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Pro Pro Phe Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:63:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Pro Pro Gly Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:64:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Pro Pro Ile Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:65:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Pro Pro Lys Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:66:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Pro Pro Leu Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:67:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Pro Pro Pro Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:68:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Pro Pro Val Pro Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:69:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acid residues
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY:
(ii) MOLECULE TYPE: peptide
(ix) FEATURE:
(A) NAME/KEY: Xaa
(B) LOCATION: position 5
(D) OTHER INFORMATION: equimolar mixture of 18 amino acids (all naturally occurring amino acids except tryptophan and cysteine)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Pro Pro Tyr Pro Xaa
1 5

WHAT IS CLAIMED IS:

1. A method of effecting a neuronal activity in an animal, comprising:

administering to the animal an effective amount of a neurotrophic compound having an affinity for a cyclophilin-type immunophilin, wherein the immunophilin exhibits rotamase activity and the neurotrophic compound inhibits the rotamase activity of the immunophilin.

2. The method according to claim 1, wherein the neuronal activity is selected from the group consisting of stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorder.

3. The method according to claim 2, wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorder relating to neurodegeneration.

4. The method according to claim 3, wherein the neurological disorder relating to neurodegeneration is

selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis.

5. The method according to claim 1, wherein the cyclophilin-type immunophilin is cyclophilin A.

6. The method according to claim 1, wherein the neurotrophic compound is of formula I (SEQ ID NOS. 1-2):

X-Pro-A3-A1-Pro-A2-Z I

wherein:

A3 is either a direct bond or a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

A1 and A2 are naturally occurring amino acids independently selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu),

methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

X is a pharmaceutically acceptable N-terminal; and

Z is a pharmaceutically acceptable C-terminal.

7. The method according to claim 6, wherein:

the N-terminal is acetyl;

the C-terminal is amino.

8. The method according to claim 6, wherein A3 is a direct bond (SEQ ID NO. 1).

9. The method according to claim 6, wherein A3 is a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp) (SEQ ID NO. 2).

10. The method according to claim 9, wherein A3

is proline (Pro) (SEQ ID NO. 3).

11. The method according to claim 10, wherein:

A1 is selected from the group consisting of tyrosine (Tyr) and phenylalanine (Phe); and

A2 is selected from the group consisting of alanine (Ala), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), isoleucine (Ile), lysine (Lys), leucine (Leu), proline (Pro), valine (Val) and tyrosine (Tyr) (SEQ ID NOS. 4-23).

12. A pharmaceutical composition comprising:

(i) a therapeutically effective amount of a neurotrophic compound of formula I (SEQ ID NOS. 1-2):

X-Pro-A3-A1-Pro-A2-Z I

and

(ii) a pharmaceutically acceptable carrier, wherein:

A3 is either a direct bond or a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln),

arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

A1 and A2 are naturally occurring amino acids independently selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp);

X is a pharmaceutically acceptable N-terminal; and

Z is a pharmaceutically acceptable C-terminal.

13. The pharmaceutical composition according to claim 12, wherein:

the N-terminal is acetyl; and

the C-terminal is amino.

14. The pharmaceutical composition according to claim 12, wherein A3 is a direct bond (SEQ ID NO. 1).

15. The pharmaceutical composition according to

claim 12, wherein A3 is a naturally occurring amino acid selected from the group consisting of alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asn), proline (Pro), glutamine (Gln), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tyrosine (Tyr), cysteine (Cys) and tryptophan (Trp) (SEQ ID NO. 2).

16. The pharmaceutical composition according to claim 12, wherein A3 is proline (Pro) (SEQ ID NO. 3).

17. The pharmaceutical composition according to claim 16, wherein:

A1 is selected from the group consisting of tyrosine (Tyr) and phenylalanine (Phe); and

A2 is selected from the group consisting of alanine (Ala), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), isoleucine (Ile), lysine (Lys), leucine (Leu), proline (Pro), valine (Val) and tyrosine (Tyr) (SEQ ID NOS. 4-23).

FIG. 1

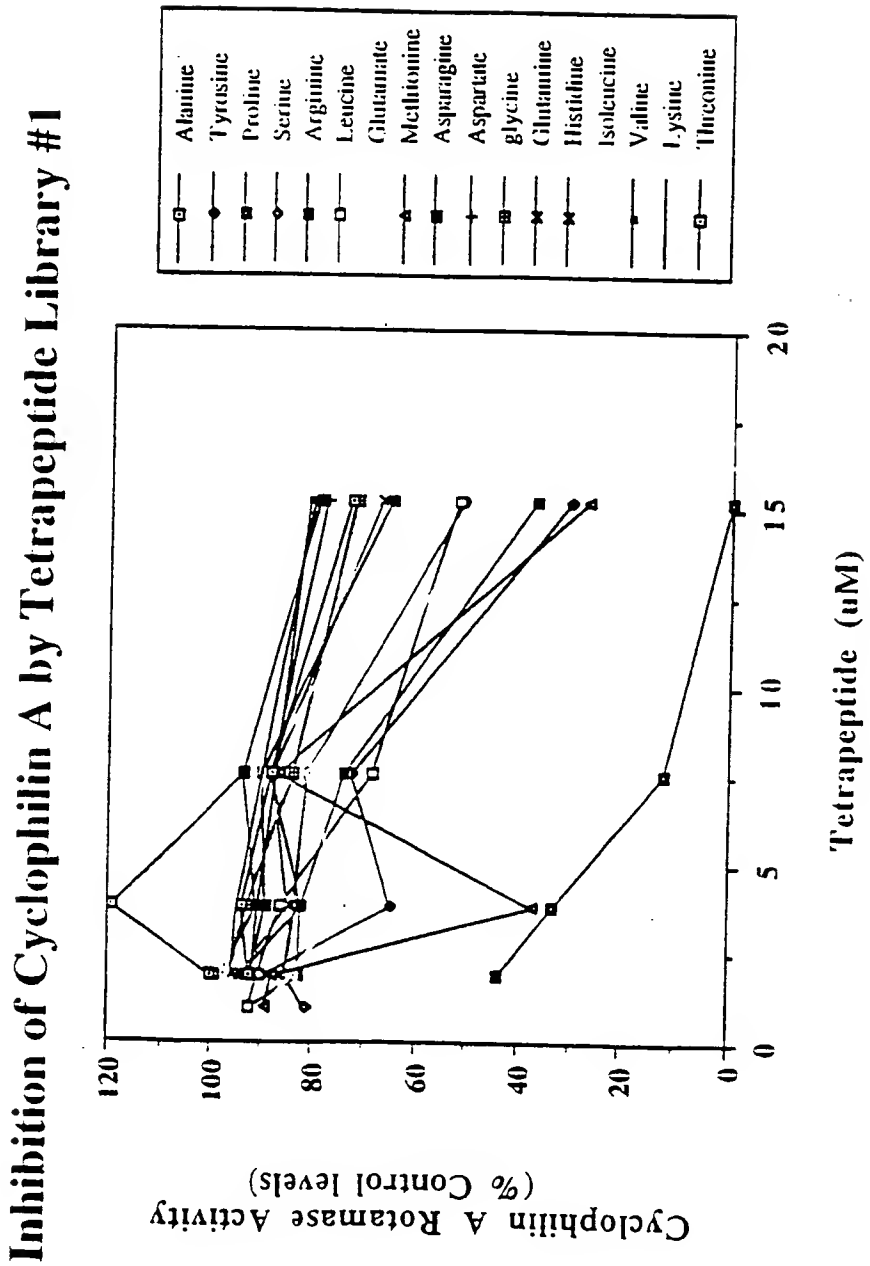

Inhibition of Cyclophilin A by Tetrapeptide Library #1
Cyclophilin A Rotamase Activity
(% Control levels)
Tetrapeptide (uM)
0
20
40
60
80
100
120
0
5
10
15
20
Alanine
Tyrosine
Proline
Serine
Arginine
Leucine
Glutamate
Methionine
Asparagine
Aspartate
glycine
Glutamine
Histidine
Isoleucine
Valine
Lysine
Threonine

FIG. 2

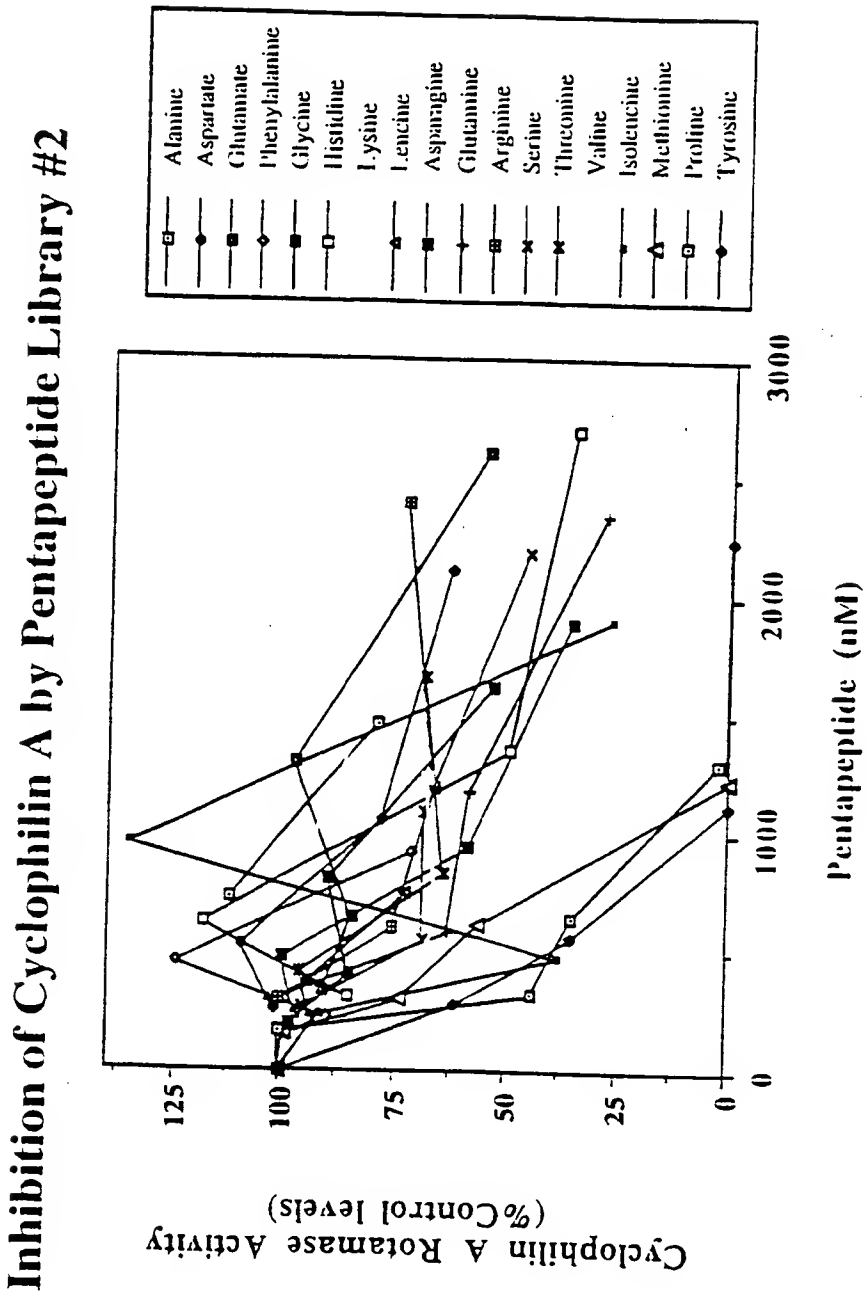

Inhibition of Cyclophilin A by Pentapeptide Library #2
Cyclophilin A Rotamase Activity
(% Control levels)
125
100
75
50
25
0
0
1000
2000
3000
Pentapeptide (nM)
Alanine
Aspartate
Glutamate
Phenylalanine
Glycine
Histidine
Lysine
Leucine
Asparagine
Glutamine
Arginine
Serine
Threonine
Valine
Isoleucine
Methionine
Proline
Tyrosine

FIG. 3

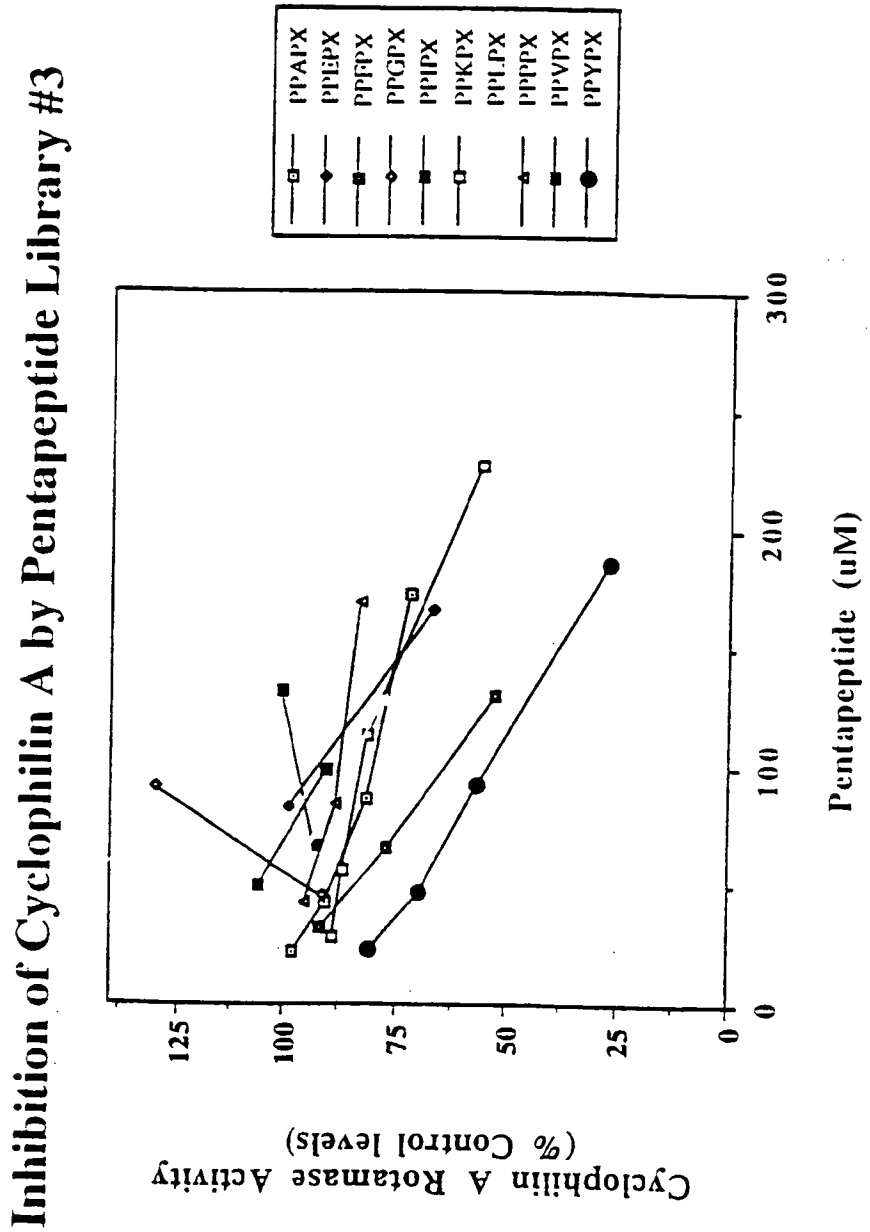
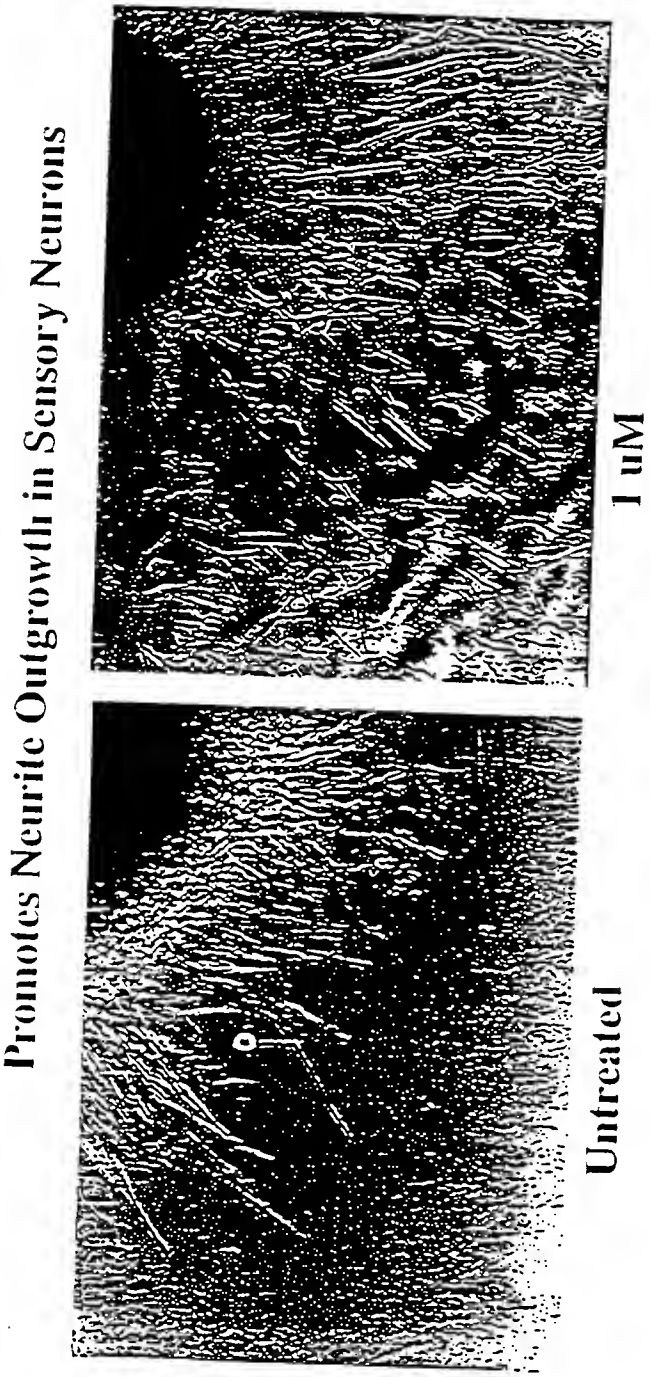

Inhibition of Cyclophilin A by Pentapeptide Library #3
Cyclophilin A Rotamase Activity
(% Control levels)
125
100
75
50
25
0
0
100
200
300
Pentapeptide (uM)
PPAPX
PPEPX
PPFPX
PPGPX
PPIPX
PPKPX
PPLPX
PPPPX
PPVPX
PPYPX

FIG. 4


Promotes Neurite Outgrowth in Sensory Neurons
1 uM
Untreated